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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 211/22, 401/12, 401/06, 405/12, 405/14, 401/14, 417/14, A61K 31/445

A1

(11) International Publication Number: WO 97/31897

(43) International Publication Date: 4 September 1997 (04.09.97)

(21) International Application Number: PCT/EP97/00585

(22) International Filing Date: 7 February 1997 (07.02.97)

(30) Priority Data:
96200525.2 29 February 1996 (29.02.96) EP
(34) Countries for which the regional or international application was filed: DE et al.

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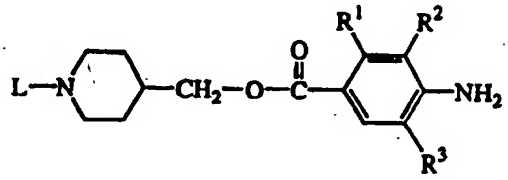
(81) Designated States: AL, AM, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL N-SUBSTITUTED 4-((4'-AMINOBENZOYL)-OXYMETHYL)-PIPERIDINES HAVING GASTRIC PROKINETIC PROPERTIES

(57) Abstract

This invention concerns the compounds of formula (I) the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein R^1 is C_{1-6}alkyloxy, C_{2-6}alkenyloxy or C_{2-6}alkynyloxy; R^2 is hydrogen or C_{1-6}alkyloxy, or when taken together R^1 and R^2 may form a bivalent radical of formula wherein in said bivalent radicals one or two hydrogen atoms may be substituted with C_{1-6}alkyl, R^3 is hydrogen or halo;



(I)

L is C_{3-6}cycloalkyl, C_{5-6}cycloalkanone, C_{2-6}alkenyl optionally substituted with aryl, or L is a radical of formula -Alk-R^4, -Alk-NR^5R^6, 1-R^6-4-piperidinyl, Alk-X-R^7, -Alk-Y-C(=O)-R^9 or -Alk-Y-C(=O)-$NR^{11}R^{12}$, wherein each Alk is C_{1-12}alkanediyl; R^4 is hydrogen, C_{1-6}alkylsulfonylamino, C_{3-6}cycloalkyl, C_{5-6}cycloalkanone, Ar-, di(Ar)methyl, Ar-oxy- or Het^1; R^5 is hydrogen or C_{1-6}alkyl; R^6 is Het^2; R^7 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-6}cycloalkyl or Ar or Het^2; X is O, S, SO_2 or NR^8; said R^8 being hydrogen, C_{1-6}alkyl or Ar; R^9 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, Ar, ArC_{1-6}alkyl, di(Ar)methyl, C_{1-6}alkyloxy or hydroxy; Y is NR^{10} or a direct bond; said R^{10} being hydrogen, C_{1-6}alkyl or Ar; R^{11} and R^{12} each independently are hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, Ar or ArC_{1-6}alkyl, or R^{11} and R^{12} combined with the nitrogen atom bearing R^{11} and R^{12} may form a pyrrolidinyl or piperidinyl ring both being optionally substituted with C_{1-6}alkyl, amino or mono or di(C_{1-6}alkyl)amino, or said R^{11} and R^{12} combined with the nitrogen bearing R^{11} and R^{12} may form a piperazinyl or 4-morpholinyl radical both being optionally substituted with C_{1-6}alkyl. Processes for preparing said products, formulations comprising said products and their use as a medicine are disclosed, in particular for treating conditions which are related to impairment of gastric emptying.

NOVEL N-SUBSTITUTED 4-((4'-AMINOBENZOYL)-OXYMETHYL)-PIPERIDINES HAVING GASTRIC PROKINETIC PROPERTIES.

The present invention is concerned with novel compounds of formula (I) having superior gastrokinetic properties. The invention further relates to methods for preparing such novel compounds, pharmaceutical compositions comprising said novel compounds as well as the use as a medicine of said compounds.

Compounds structurally related to the present novel compounds are disclosed in the prior art. WO 93/05038, published on March 18, 1993, discloses (1-butyl-4-piperidinyl)methyl 8-amino-7-chloro-1,4-benzodioxan-5-carboxylate having 5 HT_4 receptor antagonistic activity. WO 93/16072, published on August 19, 1993 discloses (1-butyl-4-piperidinyl) methyl-5-amino-6-chloro-3,4-dihydro-2*H*-1-benzopyran-8-carboxylate hydrochloride having 5 HT_4 receptor antagonistic activity. Recently, Fancelli D. et al., *Bioorganic & Medicinal Chem. Lett.*, 6:263-266, 1996, and WO-96/33186, published on October 24, 1996, disclose (1-butyl-4-piperidinyl)methyl-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate hydrochloride having 5 HT_4 receptor agonistic activity.
WO 94/29298, published on December 22, 1994 discloses 8-amino-7-chloro-1,4-benzodioxan-5-(1-butyl-4-piperidinyl)carboxylate having 5 HT_4 receptor antagonistic activity. WO 94/10174, published on May 11, 1994 discloses 5-(1-(3-pyridylmethyl)-4-piperidinyl)methyl-8-amino-7-chloro-1,4-benzo-dioxancarboxylate, [1-(2-carbo-ethoxyethyl)-4-piperidinyl]methyl-8-amino-7-chloro-1,4-benzodioxan-5-carboxylate, [1-(3-hydroxybutyl)-4-piperidinyl]methyl-8-amino-7-chloro-1,4-benzodioxan-5-carboxylate having 5 HT_4 receptor antagonistic activity. Also, WO-96/28424, published on September 19, 1996, discloses disubstituted 1,4-piperidine esters and amides having 5 HT_4 receptor antagonistic activity.

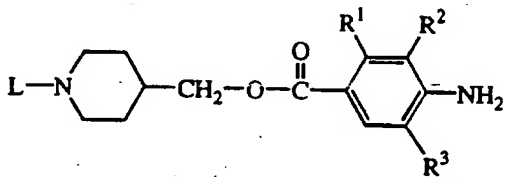
The cited prior art documents disclose compounds having 5 HT_4 receptor antagonistic activity and may generally be used in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders. In particular, these compounds are thought to be useful in the treatment of irritable bowel syndrome (IBS), especially the diarrhoea aspects of IBS by blocking the ability of 5-HT to stimulate gut motility.

The problem which this invention sets out to solve is to provide gastric prokinetic compounds, *i.e.* the actual stimulation of gastric motility.

It is generally believed that gastric prokinetic activity is correlated with 5 HT_4 receptor agonist activity, *i.e.* the opposite of 5 HT_4 antagonist activity, (King F.D. et al., *J. Med. Chem.*, 36:683-689, 1993 and Langlois M. et al., *Bioorganic & Medicinal Chem. Lett.*, 4:1433-1436, 1994).

Hence it was surprising to find that the present compounds of formula (I) show gastric prokinetic activity.

In one embodiment, this invention concerns the use of compounds of formula


(I),

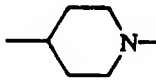
the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R^1 is C_{1-6}alkyloxy, C_{2-6}alkenyloxy or C_{2-6}alkynyloxy;
R^2 is hydrogen or C_{1-6}alkyloxy,
or when taken together R^1 and R^2 may form a bivalent radical of formula

-O-CH_2-O- (a-1),
-O-CH_2-CH_2- (a-2),
-O-CH_2-CH_2-O- (a-3),
-O-CH_2-CH_2-CH_2- (a-4),
-O-CH_2-CH_2-CH_2-O- (a-5),
-O-CH_2-CH_2-CH_2-CH_2- (a-6),

wherein in said bivalent radicals one or two hydrogen atoms may be substituted with C_{1-6}alkyl;
R^3 is hydrogen or halo;
L is C_{3-6}cycloalkyl, C_{5-6}cycloalkanone, C_{2-6}alkenyl optionally substituted with Ar, or L is a radical of formula

–Alk–R^4 (b-1),
–Alk–NR^5R^6 (b-2),


(b-3),

-Alk-X-R^7 (b-4),

-Alk-Y-C(=O)-R^9 (b-5), or

-Alk-Y-C(=O)-$NR^{11}R^{12}$ (b-6),

wherein Alk is C_{1-12}alkanediyl;

R^4 is hydrogen, C_{1-6}alkylsulfonylamino, C_{3-6}cycloalkyl, C_{5-6}cycloalkanone, Ar-, di(Ar)methyl, Ar-oxy- or Het^1;

R^5 is hydrogen or C_{1-6}alkyl;

R^6 is Het^2;

R^7 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-6}cycloalkyl, Ar or Het^2;

X is O, S, SO_2 or NR^8; said R^8 being hydrogen, C_{1-6}alkyl or Ar;

R^9 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, Ar, ArC_{1-6}alkyl, di(Ar)methyl, C_{1-6}alkyloxy or hydroxy;

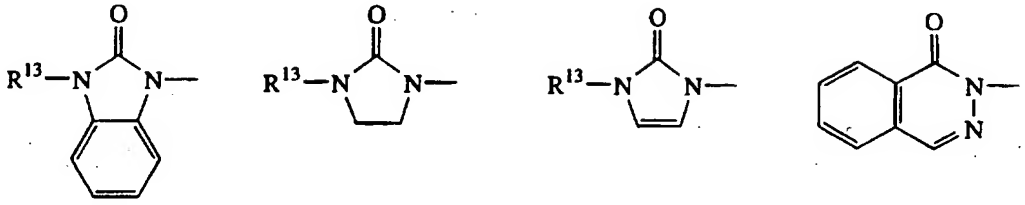
Y is NR^{10} or a direct bond; said R^{10} being hydrogen, C_{1-6}alkyl or Ar;

R^{11} and R^{12} each independently are hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, Ar or ArC_{1-6}alkyl, or R^{11} and R^{12} combined with the nitrogen atom bearing R^{11} and R^{12} may form a pyrrolidinyl or piperidinyl ring both being optionally substituted with C_{1-6}alkyl, amino or mono or di(C_{1-6}alkyl)amino, or said R^{11} and R^{12} combined with the nitrogen bearing R^{11} and R^{12} may form a piperazinyl or 4-morpholinyl radical both being optionally substituted with C_{1-6}alkyl;

each Ar being unsubstituted phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino-sulfonyl, C_{1-6}alkylcarbonyl, nitro, trifluoromethyl, amino or aminocarbonyl; and

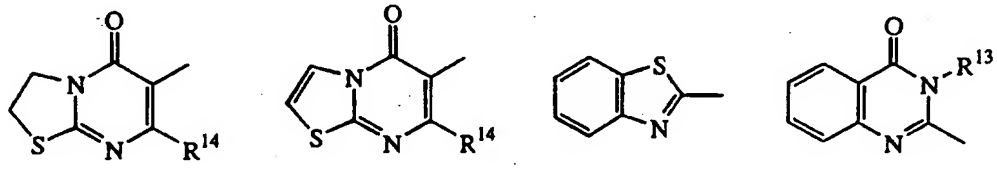
Het^1 and Het^2 each independently are selected from furan; furan substituted with C_{1-6}alkyl or halo; tetrahydrofuran; a tetrahydrofuran substituted with C_{1-6}alkyl; a dioxolane; a dioxolane substituted with C_{1-6}alkyl, a dioxane; a dioxane substituted with C_{1-6}alkyl; tetrahydropyran; a tetrahydropyran substituted with C_{1-6}alkyl; pyrrolidinyl; pyrrolidinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, or C_{1-6}alkyl; pyridinyl; pyridinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl; pyrimidinyl; pyrimidinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, amino and mono and di(C_{1-6}alkyl)amino; pyridazinyl; pyridazinyl substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, C_{1-6}alkyl or halo; pyrazinyl; pyrazinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, mono- and di(C_{1-6}alkyl)amino and C_{1-6}alkyloxycarbonyl;

Het^1 can also be a radical of formula



(c-1) (c-2) (c-3) (c-4)

Het^1 and Het^2 each independently can also be selected from the radicals of formula



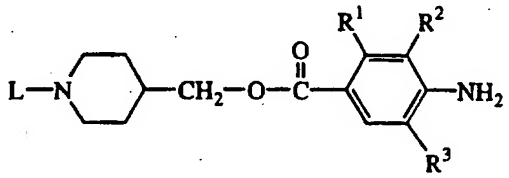
(d-1) (d-2) (d-3) (d-4)

R^{13} and R^{14} each independently are hydrogen or C_{1-4}alkyl;

with the proviso that L is other than n-butyl when R^1 and R^2 are taken together to form a bivalent radical of formula (a-2);

for the manufacture of a medicine for treating conditions involving a decreased motility of the stomach.

In another embodiment, this invention concerns novel compounds of formula (I')



(I'),

the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R^1 is C_{1-6}alkyloxy, C_{2-6}alkenyloxy or C_{2-6}alkynyloxy;

R^2 is hydrogen or C_{1-6}alkyloxy,

or when taken together R^1 and R^2 may form a bivalent radical of formula

-O-CH_2-O- (a-1),

-O-CH_2-CH_2- (a-2),

-O-CH_2-CH_2-O- (a-3),

$-O-CH_2-CH_2-CH_2-$ (a-4),

$-O-CH_2-CH_2-CH_2-O-$ (a-5),

$-O-CH_2-CH_2-CH_2-CH_2-$ (a-6),

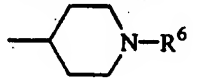
wherein in said bivalent radicals one or two hydrogen atoms may be substituted with C_{1-6}alkyl;

R^3 is hydrogen or halo;

L is C_{3-6}cycloalkyl, C_{5-6}cycloalkanone, C_{2-6}alkenyl optionally substituted with Ar, or L is a radical of formula

$-Alk-R^4$ (b-1),

$-Alk-NR^5R^6$ (b-2),

 (b-3),

$-Alk-X-R^7$ (b-4),

$-Alk-Y-C(=O)-R^9$ (b-5), or

$-Alk-Y-C(=O)-NR^{11}R^{12}$ (b-6),

wherein Alk is C_{1-12}alkanediyl;

R^4 is hydrogen, C_{1-6}alkylsulfonylamino, C_{3-6}cycloalkyl, C_{5-6}cycloalkanone, Ar-, di(Ar)methyl, Ar-oxy- or Het^1;

R^5 is hydrogen or C_{1-6}alkyl;

R^6 is Het^2;

R^7 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-6}cycloalkyl, Ar or Het^2;

X is O, S, SO_2 or NR^8; said R^8 being hydrogen, C_{1-6}alkyl or Ar;

R^9 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, Ar, ArC_{1-6}alkyl, di(Ar)methyl, C_{1-6}alkyloxy or hydroxy;

Y is NR^{10} or a direct bond; said R^{10} being hydrogen, C_{1-6}alkyl or Ar;

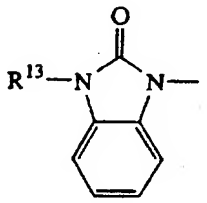
R^{11} and R^{12} each independently are hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, Ar or ArC_{1-6}alkyl, or R^{11} and R^{12} combined with the nitrogen atom bearing R^{11} and R^{12} may form a pyrrolidinyl or piperidinyl ring both being optionally substituted with C_{1-6}alkyl, amino or mono or di(C_{1-6}alkyl)amino, or said R^{11} and R^{12} combined with the nitrogen bearing R^{11} and R^{12} may form a piperazinyl or 4-morpholinyl radical both being optionally substituted with C_{1-6}alkyl;

each Ar being unsubstituted phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, aminosulfonyl, C_{1-6}alkylcarbonyl, nitro, trifluoromethyl, amino or aminocarbonyl; and

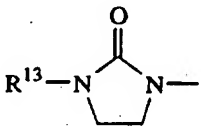
Het^1 and Het^2 each independently are selected from furan; furan substituted with C_{1-6}alkyl or halo; tetrahydrofuran; a tetrahydrofuran substituted with C_{1-6}alkyl; a dioxolane; a dioxolane substituted with C_{1-6}alkyl, a dioxane; a dioxane substituted

with C_{1-6}alkyl; tetrahydropyran; a tetrahydropyran substituted with C_{1-6}alkyl; pyrrolidinyl; pyrrolidinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, or C_{1-6}alkyl; pyridinyl; pyridinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl; pyrimidinyl; pyrimidinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, amino and mono and di(C_{1-6}alkyl)amino; pyridazinyl; pyridazinyl substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, C_{1-6}alkyl or halo; pyrazinyl; pyrazinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, mono- and di(C_{1-6}alkyl)amino and C_{1-6}alkyloxycarbonyl;

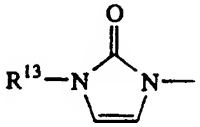
Het^1 can also be a radical of formula



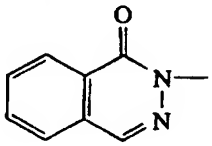
(c-1)



(c-2)

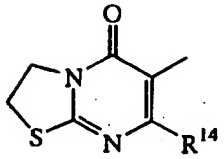


(c-3)

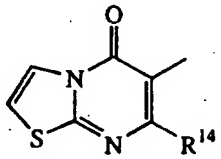


(c-4)

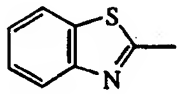
Het^1 and Het^2 each independently can also be selected from the radicals of formula



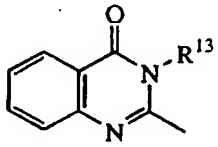
(d-1)



(d-2)



(d-3)



(d-4)

R^{13} and R^{14} each independently are hydrogen or C_{1-4}alkyl;

with the proviso that R^4 is other than hydrogen, phenyl, 4-fluorophenyl, 4-methylphenyl or 4-methoxyphenyl when R^1 and R^2 are taken together to form a bivalent radical of formula -O-CH_2-CH_2-O-; or L is other than n-butyl when R^1 and R^2 are taken together to form a bivalent radical of formula (a-2) or (a-4).

The proviso is intended to exclude compounds E1, E2, E22 - E25, E27, E28, E30, E39 - E42 which are disclosed in WO-93/05038, compound E6 disclosed in WO-93/16072 and compound FCE 29029A disclosed in WO-96/33186.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl and the like; C_{1-6}alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof having 5 or 6 carbon atoms, such as, for example, 2-methylbutyl, pentyl, hexyl and the like; C_{2-6}alkenyl defines straight and branched chain unsaturated hydrocarbon radicals having from 2 to 6 carbon atoms, such as ethenyl, propenyl, butenyl, pentenyl or hexenyl; C_{2-6}alkynyl defines straight and branched chain hydrocarbon radicals having from 2 to 6 atoms containing a triple bond, such as ethynyl, propynyl, butynyl, pentynyl or hexynyl; C_{1-5}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 1 to 5 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl and the like; and C_{1-6}alkanediyl is meant to include C_{1-5}alkanediyl and the higher homologues thereof having 6 carbon atoms, such as, for example, 1,6-hexanediyl and the like.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms which the compounds of formula (I) or (I') may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration. Stereochemically isomeric forms of the compounds of formula (I) or (I') are obviously intended to be embraced within the scope of this invention.

Some of the compounds of formula (I) or (I') may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. For instance, compounds of formula (I) or (I') wherein Het^1 or Het^2 is pyrimidinyl substituted with hydroxy, may exist in their corresponding tautomeric form.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) or (I') are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such

as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) or (I') as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

The *N*-oxide forms of the compounds of formula (I) or (I') are meant to comprise those compounds of formula (I) or (I') wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein the piperidine-nitrogen is *N*-oxidized.

Whenever used hereinafter, the term "compounds of formula (I) or (I')" is meant to also include their *N*-oxide forms, their pharmaceutically acceptable addition salts, and their stereochemically isomeric forms.

A first interesting group of compounds consists of compounds of formula (I') wherein R^1 and R^2 are taken together to form a radical of formula (a-2) or (a-3), wherein optionally one or two hydrogen atoms are substituted with methyl; and R^3 is halo.

A second group of interesting compounds are those compounds of formula (I') wherein R^1 is methoxy, R^2 is hydrogen and R^3 is chloro.

A particular group of compounds are those compounds of formula (I') wherein L is a radical of formula (b-1) and R^4 is Het^1 or substituted phenyloxy.

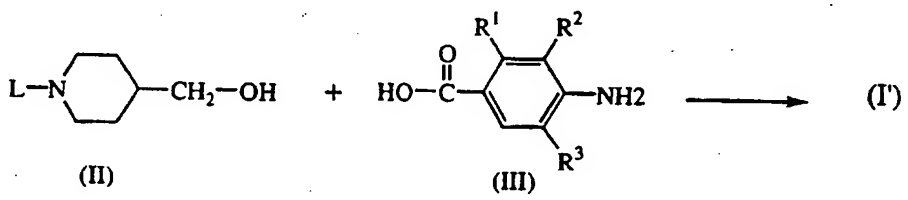
Another particular group of compounds are those compounds formula (I') wherein L is a radical of formula (b-2) or (b-3) and R^6 is Het^2.

Preferred compounds are those wherein R^1 and R^2 are taken together to form a radical of formula (a-2) or (a-3), wherein optionally one or two hydrogen atoms are substituted with methyl; R^3 is chloro; L is a radical of formula (b-1), (b-2) or (b-3) wherein R^4 is substituted phenyloxy, R^5 is hydrogen and R^6 is Het^2; in particular R^4 is phenyloxy

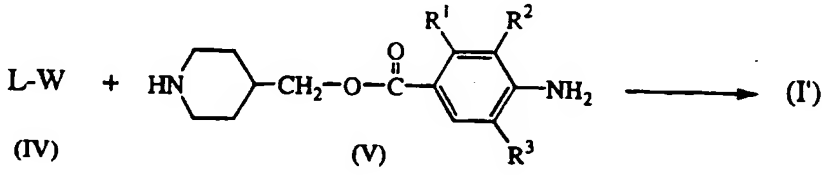
substituted with halo and R^6 is pyrazidinyl or imidazolyl optionally substituted with hydroxy or C_{1-6}alkyl.

Most preferred are
[1-[2-[(3-methyl-2-pyrazinyl)amino]ethyl]-4-piperidinyl]methyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; or
[1-[2-[2,3-dihydro-3-(1-methylethyl)-2-oxo-1*H*-imidazol-1-yl]ethyl]-4-piperidinyl]-methyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; or
[1-[2-[(3-methyl-2-pyrazinyl)amino]ethyl]-4-piperidinyl]methyl 8-amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-carboxylate; or
[1-[1-(3-methyl-2-pyrazinyl)-4-piperidinyl]-4-piperidinyl]methyl 8-amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-carboxylate; and the pharmaceutically acceptable acid addition salts and the stereo isomeric forms thereof.

The compounds of formula (I') may generally be prepared by reacting an intermediate of formula (II) with a carboxylic acid derivative of formula (III) or a reactive functional derivative thereof, such as, for example, an acid chloride or a carbonyl imidazole derivative. Said esterbond formation may be performed by stirring the reactants in an appropriate solvent in the presence of a base, such as sodium imidazolide.



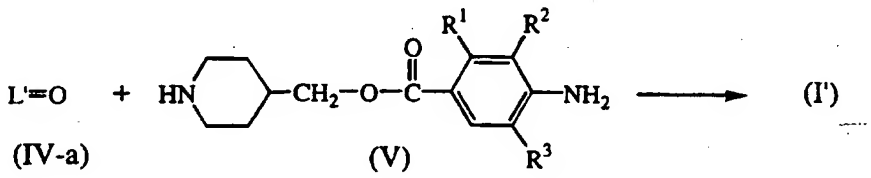
Another way of preparing compounds of formula (I') is by *N*-alkylating an intermediate of formula (V) with an intermediate of formula (IV), wherein W is an appropriate leaving group such as, for example, a halogen, e.g. chloro or bromo, or a sulfonyloxy leaving group, e.g. methanesulfonyloxy or benzenesulfonyloxy.



Said *N*-alkylation reaction can be performed in a reaction-inert solvent such as, for example, a dipolar aprotic solvent, e.g. *N,N*-dimethylformamide, or a ketone, e.g. methyl isobutylketone, and in the presence of a suitable base such as, for example,

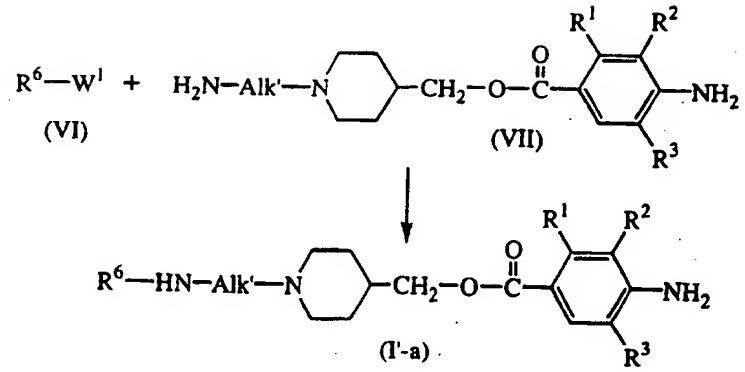
sodium carbonate, sodium hydrogen carbonate or triethylamine. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature.

Alternatively, an intermediate of formula (V) is reductively *N*-alkylated with an intermediate of formula L'=O (IV-a), wherein L'=O represents a derivative of formula L–H wherein two geminal hydrogen atoms are replaced by oxygen, following "art-known reductive *N*-alkylation procedures".

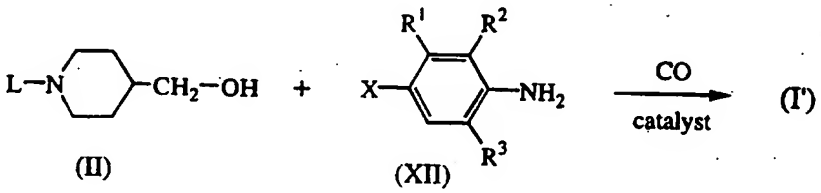


Said reductive *N*-alkylation may be performed in a reaction-inert solvent such as, for example, dichloromethane, ethanol, toluene or a mixture thereof, and in the presence of a reducing agent such as, for example, a borohydride, e.g. sodium borohydride, sodium cyanoborohydride or triacetoxy borohydride. It may also be convenient to use hydrogen as a reducing agent in combination with a suitable catalyst such as, for example, palladium-on-charcoal or platinum-on-charcoal. In case hydrogen is used as reducing agent, it may be advantageous to add a dehydrating agent to the reaction mixture such as, for example, aluminium *tert*-butoxide. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products, it may also be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g., thiophene or quinoline-sulphur. To enhance the rate of the reaction, the temperature may be elevated in a range between room temperature and the reflux temperature of the reaction mixture and optionally the pressure of the hydrogen gas may be raised.

Further, compounds of formula (I') wherein L is Alk'-NHR^6 and Alk' is C_{2-6}alkanediyl, said compounds being represented by formula (I'-a), can be prepared by treating intermediates (VII) with intermediates (VI), wherein W^1 is a suitable leaving group such as, a halo, e.g. chloro, bromo or iodo, or an alkylthio, e.g. methylthio, in an appropriate solvent e.g. acetonitrile or dimethylacetamide.



Also, compounds of formula (I') may be prepared by carbonylation of an intermediate of formula (XII), wherein X is bromo or iodo, in the presence of an intermediate of formula (II).



Said carbonylation reaction is carried out in a reaction-inert solvent such as, e.g. acetonitrile or tetrahydrofuran, in the presence of a suitable catalyst and a tertiary amine such as, e.g. triethylamine, and at a temperature ranging between room temperature and the reflux temperature of the reaction mixture. Suitable catalysts are, for instance, palladium-on-carbon, palladium(triphenylphosphine) complexes or Raney nickel. Carbon monoxide is administered at atmospheric pressure or at an increased pressure. Analogous carbonylation reactions are described in Chapter 8 of "Palladium reagents in organic syntheses", Academic Press Ltd., Benchtop Edition 1990, by Richard F. Heck; and the references cited therein.

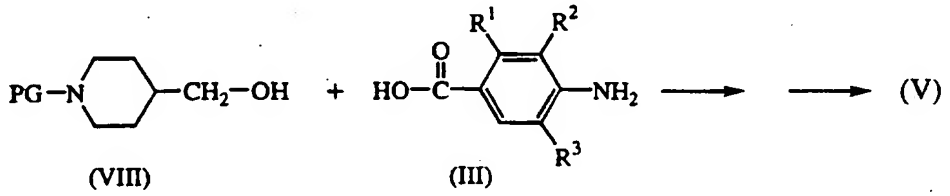
The compounds of formula (I) may further be prepared by converting compounds of formula (I) into each other according to art-known group transformation reactions.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example,

benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

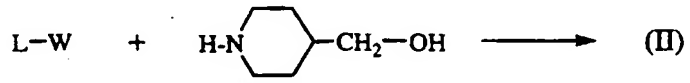
The starting materials and some of the intermediates are known compounds and are commercially available or may be prepared according to conventional reaction procedures generally known in the art. For instance, some intermediates of formula (III) have been described in EP-0,389,037.

An intermediate of formula (V) may be prepared by reacting an intermediate of formula (VIII), wherein PG represents an appropriate protective group, such as, for example, a *tert*-butoxycarbonyl, a benzyl group or a photoremovable group, with an acid of formula (III) or an appropriate reactive functional derivative thereof, and subsequent deprotection of the thus formed intermediate, *i.e.* removal of PG by art-known methods.



(VIII) (III)

An intermediate of formula (II) may be prepared by reacting an intermediate of formula (IX), which may be prepared by deprotecting an intermediate of formula (VIII), with an intermediate of formula (IV).

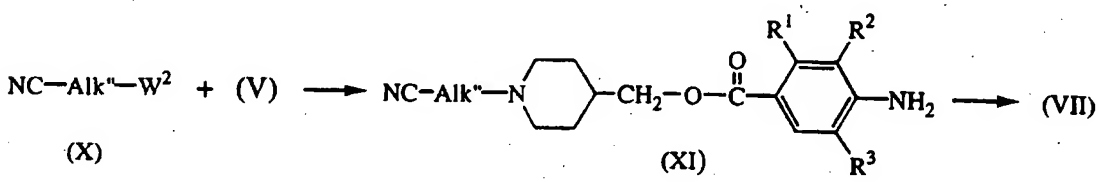


(IV) (IX)

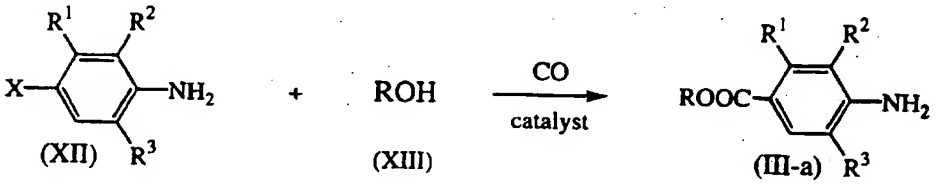
In some cases, it may be appropriate to protect the primary alcohol functionality during the reactionsequence starting from intermediate (IX) to intermediate (II). Protecting groups for primary alcohol functionalities are art-known. These protecting groups may then be removed at the appropriate time during the further synthesis.

Intermediates of formula (VII) can be prepared by treating an intermediate (V) with an intermediate of formula (X), wherein W^2 is an appropriate leaving group such as, for example, a halogen, e.g. chloro or bromo, or a sulfonyloxy leaving group, e.g. methane-

sulfonyloxy or benzenesulfonyloxy, and Alk" is C_{1-5}alkanediyl, according to the previously described *N*-alkylation method, and subsequent reduction of intermediate (XI) with an appropriate reducing agent such as, e.g. Raney nickel, in a reaction-inert solvent e.g. THF and in the presence of hydrogen.



Ester derivatives of intermediates of formula (III) can generally be prepared by carbonylating an intermediate of formula (XII), wherein X is bromo or iodo in the presence of an alcohol of formula (XIV), wherein R is C_{1-6}alkyl.



Said carbonylation reaction is carried out in a reaction-inert solvent such as, e.g. acetonitrile or tetrahydrofuran, in the presence of a suitable catalyst and potassium acetate or a tertiary amine such as, e.g. triethylamine, and at a temperature ranging between room temperature and the reflux temperature of the reaction mixture. Suitable catalysts are, for instance, palladium-on-carbon or Raney nickel. Carbon monoxide is administered at atmospheric pressure or at an increased pressure. Analogous carbonylation reactions are described in Chapter 8 of "Palladium reagents in organic syntheses", Academic Press Ltd., Benchtop Edition 1990, by Richard F. Heck; and the references cited therein.

The compounds of formula (I) as prepared in the hereinabove described processes may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting

materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I) or (I'), the *N*-oxide forms, the pharmaceutically acceptable salts and stereoisomeric forms thereof possess favourable intestinal motility stimulating properties. In particular the present compounds show significant gastric emptying activity as is evidenced in example C.1, the "Gastric emptying of an acaloric liquid meal delayed by administration of lidamidine in conscious dogs"-test.

In view of the capability of the compounds of the present invention to enhance the gastrointestinal motility, and in particular to activate gastric emptying, the subject compounds are useful to treat conditions related to a hampered or impaired gastric emptying and more generally to treat conditions related to a hampered or impaired gastrointestinal transit.

The compounds of formula (I) also are believed to have a beneficial effect on the pressure of the LES (Lower Esophagus Sphincter).

Some of the compounds of the present invention also have colon motility stimulating properties.

In view of the utility of the compounds of formula (I), it follows that the present invention also provides a method of treating warm-blooded animals, including humans, (generally called herein patients) suffering from conditions related to a hampered or impaired gastric emptying or more generally suffering from conditions related to a hampered or impaired gastrointestinal transit. Consequently a method of treatment is provided for relieving patients suffering from conditions, such as, for example, gastro-oesophageal reflux, dyspepsia, gastroparesis, constipation, post-operative ileus, and intestinal pseudo-obstruction. Gastroparesis can be brought about by an abnormality in the stomach or as a complication of diseases such as diabetes, progressive systemic sclerosis, anorexia nervosa and myotonic dystrophy. Constipation can result form conditions such as lack of intestinal muscle tone or intestinal spasticity. Post-operative ileus is an obstruction or a kinetic impairment in the intestine due to a disruption in muscle tone following surgery. Intestinal pseudo-obstruction is a condition characterized by constipation, colicky pain, and vomiting, but without evidence of physical obstruction. The compounds of the present invention can thus be used either

to take away the actual cause of the condition or to relief the patients from symptoms of the conditions. Dyspepsia is an impairment of the function of digestion, that can arise as a symptom of a primary gastrointestinal dysfunction, especially a gastrointestinal dysfunction related to an increased muscle tone or as a complication due to other disorders such as appendicitis, galbladder disturbances, or malnutrition.

The symptoms of dyspepsia may also arise due to the intake of chemical substances, e.g. SSRI's.

Hence, the use of a compound of formula (I') as medicine is provided, and in particular the use of a compound of formula (I) for the manufacture of a medicine for treating conditions involving a decreased motility of the stomach. Both prophylactic and therapeutic treatment are envisaged.

To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions.

These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In general it is contemplated that a therapeutically effective amount would be from about 0.001 mg/kg to about 10 mg/kg body weight, preferably from about 0.02 mg/kg to about 5 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between one to four intakes per day.

The following examples are provided for purposes of illustration, not limitation.

Experimental part.

Hereinafter "THF" means tetrahydrofuran, "DIPE" means diisopropylether, "DCM" means dichloromethane, "DMF" means *N,N*-dimethylformamide and "ACN" means acetonitrile.

A. Preparation of the intermediates.

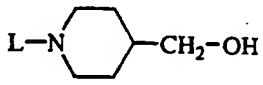
Example A.1

A mixture of 1-(2-amino-ethyl)-4-piperidinemethanol (5.2 g), 2-chloro-3-methyl-pyrazine (5.0 g) and CaO (4.5 g) was stirred for 20 hours at 120°C. The reaction mixture was cooled and purified by column chromatography over silica gel (eluent : CH_2Cl_2/(CH_3OH/NH_3) 92/8). The pure fractions were collected and the solvent was evaporated, yielding 2.3 g (29%) 1-[2-[(3-methyl-2-pyrazinyl)amino]-ethyl]-4-piperidinemethanol (intermediate 1).

Example A.2

A mixture of 1-(2-chloroethyl)-1,3-dihydro-3-(1-methylethyl)-2*H*-imidazol-2-one (12 g), 4-piperidinemethanol hydrochloride (9.1 g), *N*,*N*-diethylethanamine (21 ml) and KI (catalytic amount) in DMF (200 ml) was stirred for 20 hours at 70°C. The reaction mixture was cooled and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/(CH_3OH/NH_3) 95/5). The pure fractions were collected and the solvent was evaporated, yielding 6.9 g (43%) 1,3-dihydro-1-[2-[4-(hydroxymethyl)-1-piperidinyl]ethyl]-3-(1-methylethyl)-2*H*-imidazol-2-one (intermediate 3).

Table 1 :



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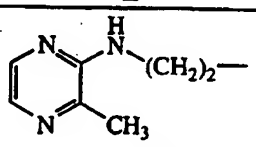
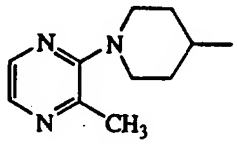
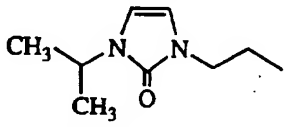
1	A.1		-
2	A.1		mp. 126.7°C
3	A.2		-
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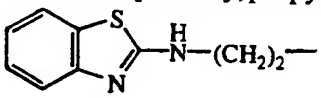
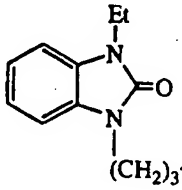
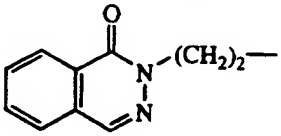
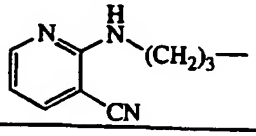
5	A.2		-
6	A.2		-
7	A.2		-
8	A.2		-

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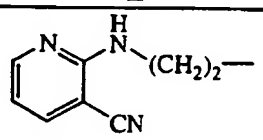
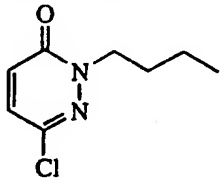
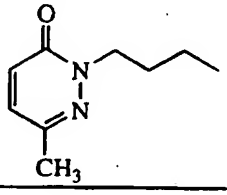
9	A.2		-
16	A.2		-
17	A.2		-

Example A.3

a) Sodium hydride (5.8 g) was added to a solution of 1,1-dimethylethyl 1-piperidine-4-methanolcarboxylate (25 g) in THF (800 ml). The mixture was stirred and refluxed for 3 hours (H_2 gas evolution), then cooled (solution I). 1,1'-Carbonylbis-1*H*-imidazole (19.5 g) was added to a suspension of 4-amino-5-chloro-2-methoxybenzoic acid (24 g) in ACN (800 ml), stirred at room temperature. This mixture was stirred for 2 hours at room temperature (solution II). At room temperature, solution (II) was poured out into solution (I) and the reaction mixture was stirred for 20 hours at room temperature. Water (± 10 ml) was added. The organic solvent was evaporated. The residue was partitioned between DCM and H_2O. The insoluble solid was filtered off. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was crystallized from ACN (0°C). The precipitate was filtered off and dried, filtered and the solvent was evaporated. The residue was crystallized from ACN. The precipitate was filtered off and dried (vacuum; 50°C), yielding 20 g (42%) 1,1-dimethylethyl 4-[[(4-amino-5-chloro-2-methoxy-benzoyl)oxy]methyl]-1-piperidine-carboxylate (intermediate 10).

b) A mixture of intermediate 10 (18 g) in HCl (25 ml) and THF (250 ml) was stirred for 30 minutes at 70°C. The reaction mixture was cooled, alkalized with aqueous ammonia and the layers were separated. The aqueous layer was extracted twice with THF. The combined organic layers were dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/(CH_3OH/NH_3) 90/10). The pure fractions were collected and the solvent was evaporated. The residue (10 g) was dissolved in $CHCl_3$, washed with aqueous

ammonia, dried, filtered and the solvent was evaporated. The residue was suspended in DIPE, filtered off and dried, yielding 8.5 g (65%) 4-piperidinylmethyl 4-amino-5-chloro-2-methoxybenzoate (intermediate 11).

In a similar way, 4-piperidinylmethyl 4-amino-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofurancarboxylate (intermediate 12) and 4-piperidinylmethyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate(intermediate 13) were synthesized.

Example A.4

a) A mixture of chloroacetonitrile (2.15 ml) and (4-piperidinyl)-methyl 8-amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-carboxylate (11 g) in *N,N*-diethylethanamine (7 ml) and DMF (150 ml) was stirred at 60°C until the reaction was complete. Then, the mixture was cooled. The solvent was evaporated. The residue was partitioned between DCM and water. The separated organic layer was dried, filtered and the solvent was evaporated. The residue was crystallized from ACN and the precipitate was filtered off and dried (vacuum, 50°C), yielding 6.6 g (53%) [1-(cyanomethyl)-4-piperidinyl]-methyl 8-amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-carboxylate (intermediate 14).

b) A mixture of intermediate 14 (6 g) in THF (250 ml) was hydrogenated with Raney nickel (3 g) as a catalyst. After uptake of hydrogen (2 equivalents), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent CH_2Cl_2/(CH_3OH/NH_3) 90/10). The pure fractions were collected and the solvent was evaporated, yielding 4 g (68%) [1-(2-amino-ethyl)-4-piperidinyl]methyl 8-amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-carboxylate (intermediate 15).

Example A.5

a) $CaCO_3$ (3.9 g) was added to a mixture of 1,3-benzodioxol-4-amine (4.11 g) in DCM (40 ml) and CH_3OH (20 ml). This mixture was stirred at room temperature. *N,N,N*-trimethyl benzenemethanaminium dichloroiodate (11.5 g) was added portionwise at room temperature. The resulting reaction mixture was stirred for 15 minutes at room temperature. The mixture was diluted with water. The layers were separated. The aqueous phase was extracted with DCM. The combined organic layers were washed with water, dried, filtered and the solvent evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/hexane 80/20). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried, yielding 3.5 g (46.9%) of 7-iodo-1,3-benzodioxol-4-amine (intermediate 18).

b) Acetic anhydride (14.25 ml) was added dropwise to a mixture of intermediate 18 (36.6 g) in acetic acid (500 ml), stirred at room temperature. The reaction mixture was stirred for 15 minutes at room temperature. The reaction mixture was poured out into water (500 ml). The precipitate was filtered, washed with water, then dried, yielding 39.29 g (92.6%) of *N*-(7-iodo-1,3-benzodioxol-4-yl)acetamide (intermediate 19).

c) A mixture of intermediate 19 (38.8 g), potassium acetae (20 g) and Pd/C (10 %; 2 g) in CH_3OH (500 ml) was stirred at 150°C under 4.9×10^6 Pa (50 kg) pressure of CO, during 16 hours. The reaction mixture was cooled, filtered over dicalite, and the filtrate was evaporated. The residue was diluted with water, then extracted three times with DCM. The combined organic layers were dried, filtered and the solvent evaporated. The residue was dissolved in acetic acid (250 ml) and acetic anhydride (6 ml) was added dropwise. The mixture was stirred for 30 minutes at room temperature, then diluted with water (250 ml) and the resulting precipitate was filtered off, washed with water, then dried, yielding 19.4 g (64.7%) of methyl 7-(acetylamino)-1,3-benzodioxole-4-carboxylate (intermediate 20).

d) A mixture of intermediate 20 (18.5 g) and NCS (11.4 g) in ACN (130 ml) was stirred and refluxed for one hour. The reaction mixture was cooled. The precipitate was filtered off, washed with ACN, with DIPE, then dried, yielding 18.2 g (87%) of methyl 7-(acetylamino)-6-chloro-1,3-benzodioxole-4-carboxylate (intermediate 21).

e) Intermediate 21 (18.2 g) was added to a solution of KOH (37.6 g) in water (380 ml). The resulting reaction mixture was stirred and refluxed for 3 hours. The mixture was cooled, acidified with hydrochloric acid, and the resulting precipitate was filtered off, washed with water, suspended in ACN, filtered off, then dried, yielding 14 g (> 95%) of 7-amino-6-chloro-1,3-benzodioxole-4-carboxylic acid (intermediate 22).

f) A mixture of intermediate 22 (1 g) and 1,1'-carbonylbis-1*H*-imidazole (0.8 g) in ACN (80 ml) was stirred for 3 hours at room temperature. The solvent was evaporated. The residue was partitioned between water and DCM. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was suspended in DIPE, filtered off, then dried (vacuum), yielding 0.8 g (75%) of 1-[(7-amino-6-chloro-1,3-benzodioxol-4-yl)carbonyl]-1*H*-imidazole (intermediate 23).

B. Preparation of the final compounds.

Example B.1

A mixture of 1-chloro-(4-fluorophenoxy)propane (2.3 g), intermediate 11 (3 g) and *N*,*N*-diethylethanamine (2.8 ml) in DMF (50 ml) was stirred for 48 hours at 70°C. The reaction mixture was cooled and the solvent was evaporated. The residue was partitioned between DCM and water. The organic layer was separated, washed with

water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from ACN (0°C). The precipitate was filtered off and dried (vacuum; 50°C), yielding 1.17 g (26%) [1-[3-(4-fluorophenoxy)propyl]-4-piperidinyl]methyl 4-amino-5-chloro-2-methoxybenzoate (compound 1, mp. 140.0°C).

Example B.2

Sodium hydride (0.4 g) was added to a solution of intermediate 1 (2.3 g) in THF (65 ml). The mixture was stirred and refluxed for 3 hours, then cooled (solution I). 1,1'-Carbonylbis-1*H*-imidazole (1.65 g) was added to a solution of 4-amino-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofurancarboxylic acid (2.42 g) in ACN (65 ml), stirred at room temperature. This mixture was stirred for 2 hours at room temperature. The solvent was evaporated. The residue was dissolved in THF (65 ml) (solution II). At room temperature, solution (II) was poured out into solution (I) and the reaction mixture was stirred for 90 minutes at room temperature. The solvent was evaporated. The residue was partitioned between DCM and water. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 95/5). The pure fractions were collected and the solvent was evaporated. The residue was solidified in DIPE. The precipitate was filtered off and dried vacuum; 50°C), yielding 1.58 g (33%) [1-[2-[(3-methyl-2-pyrazinyl)amino]ethyl]-4-piperidinyl]methyl 4-amino-5-chloro-2,3-dihydro-2,2-dimethyl-7-benzofurancarboxylate (compound 6).

Example B.3

A mixture of intermediate 15 (2 g) and 4-hydroxy-2-methylthiopyrimidine (0.86 g) in ACN (50 ml) was stirred and refluxed for 24 hours. 4-Hydroxy-2-methylthiopyrimidine (0.28 g) was added. The mixture was stirred and refluxed for 6 hours, cooled and the solvent was evaporated. The residue was taken up in DCM and water. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : $CH_2Cl_2/CH_3OH/(CH_3OH/NH_3)$ 88/10/2). The desired fractions were collected and the solvent was evaporated. The residue was repurified by column chromatography over silica gel (eluent : $CH_2Cl_2/(CH_3OH/NH_3)$ 90/10). The pure fractions were collected and the solvent was evaporated. The residue was suspended in DIPE, filtered off and dried (vacuum, 60°C), yielding 0.7 g (27%) [1-[2-[(1,4-dihydro-4-oxo-2-

pyrimidinyl)amino]-ethyl]-4-piperidinyl]methyl 8-amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-carboxylate (compound 15).

Example B.4

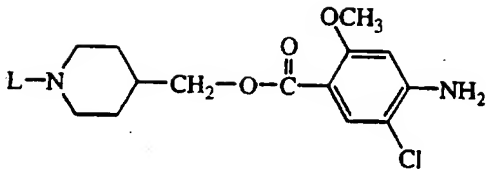
A mixture of intermediate 15 (2 g), 2-chloro-4-hydroxyquinazoline (1.9 g), *N,N*-dimethylacetamide (0.3 ml) and calciumoxide (0.4 g) was stirred for 1 hour at 140°C, then cooled and partitioned between water and DCM (+ methanol). The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/(CH_3OH/NH_3) 95/5). The desired fractions were collected and the solvent was evaporated. The residue was suspended in DIPE, filtered off, then dried (vacuum, 60°C), yielding 1.4 g (50%) [1-[2-[(1,4-dihydro-4-oxo-2-quinazolinyl)amino]ethyl]-4-piperidinyl]methyl 8-amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-carboxylate (compound 19).

Example B.5

1*H*-imidazole (2.72 g) was added to a solution of 6-chloro-2-[3-[4-(hydroxymethyl)-1-piperidinyl]propyl]-3(2*H*) -pyridazinone (2.62 g) in THF (100 ml). NaH (60%, 0.4 g) was added, under nitrogen atmosphere. The mixture was stirred for 10 minutes. 1-[(4-Amino-5-chloro-2,3-dihydro-7-benzofuranyl)carbonyl]-1*H*-imidazole (2.64 g) was added and the resulting reaction mixture was stirred for 15 minutes at room temperature. The solvent was evaporated. The residue was partitioned between water and DCM. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/hexane/(CH_3OH/NH_3) 50/45/5). The desired fractions were collected and the solvent was evaporated. The residue was crystallized from DIPE with a drop of ACN. The precipitate was filtered off, washed and dried, yielding 1.88 g (39%) of [1-[3-(3-chloro-6-oxo-1(6*H*)-pyridazinyl)propyl]-4-piperidinyl]methyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate (compound 21, mp: 137 °C)
In a similar way, [1-[3-(3-methyl-6-oxo-1(6*H*)-pyridazinyl)propyl]-4-piperidinyl]-methyl 7-amino-6-chloro-1,3-benzodioxole-4-carboxylate (compound 22) was also prepared.

Tables 2 to 4 list the compounds that were prepared according to one of the above Examples.

Table 2 :



Co. No.	Ex. No.	L	Physical data
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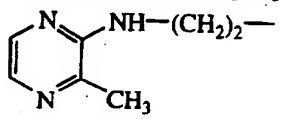
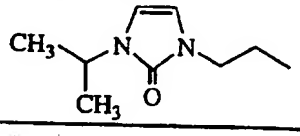
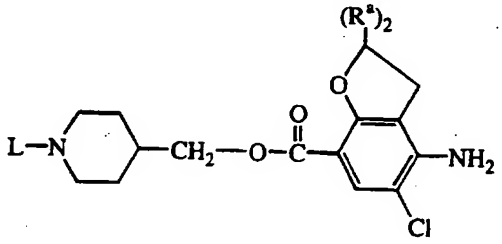
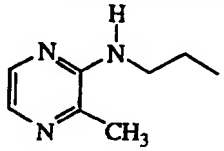
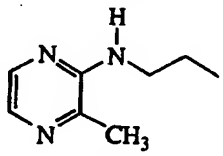
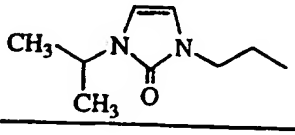
2	B.2		mp. 103.3°C
3	B.2		mp. 130.3°C

Table 3 :



Co. No.	Ex. No.	L	R^a	Physical data
4	B.1	3-(4-fluorophenoxy)propyl	CH_3	mp. 105.6°C
5	B.2	3-(4-fluorophenoxy)propyl	H	mp. 130.8°C
6	B.2		CH_3	mp. 126.4°C
7	B.2		H	mp. 188.3°C
8	B.2		CH_3	mp. 78.6°C

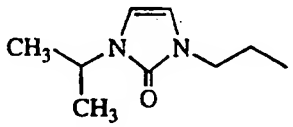
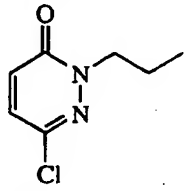
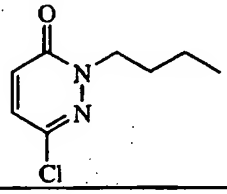
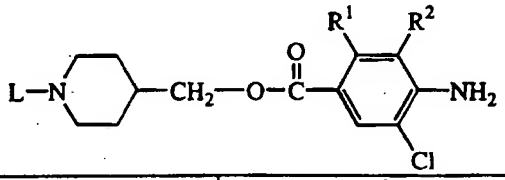
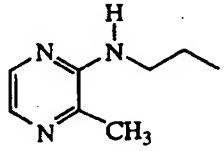
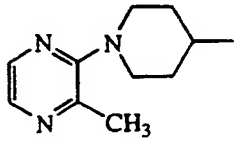
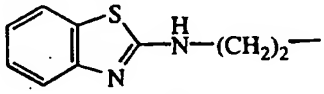
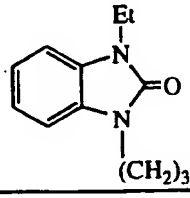
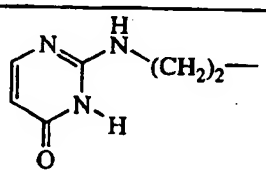
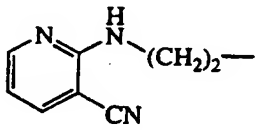
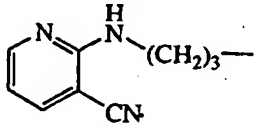
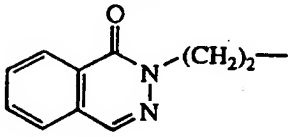
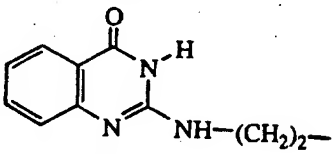
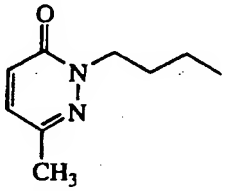
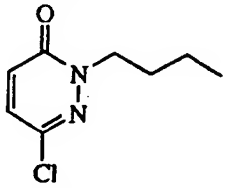
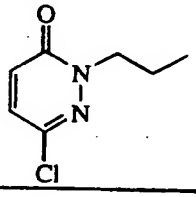
Co. No.	Ex. No.	L	R^a	Physical data
9	B.2		H	mp. 130.6°C
20	B.1		H	mp. 178°C
21	B.5		H	mp. 137°C

Table 4 :



Co. No.	Ex. No.	L	R^1 and R^2 taken together	Physical data
10	B.2	3-(4-fluorophenoxy)propyl	-O-CH_2-CH_2-O-	mp. 157.1°C ; .$C_2H_2O_4$
11	B.2		-O-CH_2CH_2-O-	mp. 121.4°C
12	B.2		-O-CH_2CH_2-O-	mp. 168.1°C
13	B.2		-O-CH_2CH_2-O-	mp. 168.5°C
14	B.2		-O-CH_2CH_2-O-	mp. 138.2°C

Co. No.	Ex. No.	L	R^1 and R^2 taken together	Physical data
15	B.3		-O-CH_2CH_2-O-	mp. 130.4°C
16	B.2		-O-CH_2CH_2-O-	-
17	B.2		-O-CH_2CH_2-O-	-
18	B.2		-O-CH_2-CH_2-O-	mp. 200.4°C ; .$C_2H_2O_4$
19	B.4		-O-CH_2CH_2-O-	mp. 145.7°C
22	B.5		-O-CH_2-O-	mp. 125°C
23	B.5		-O-$CH_2CH_2CH_2$-O-	mp. 148°C ; .$C_2H_2O_4$
24	B.5		-O-CH_2CH_2-O-	mp. 184°C ; .$C_2H_2O_4$

C. Pharmacological example.

Example C.1 :"Gastric emptying of an acaloric liquid test meal delayed by administration of lidamidine, in conscious dogs" test.

Female beagle dogs, weighing 7-14 kg, were trained to stand quietly in Pavlov frames. They were implanted with a gastric cannula under general anaesthesia and aseptic

precautions. After a median laparatomy, an incision was made through the gastric wall in the longitudinal direction between the greater and the lesser curve, 2 cm above the nerves of Latarjet. The cannula was secured to the gastric wall by means of a double purse string suture and brought out via a stab wound at the left quadrant of the hypochondrium. Dogs were allowed a recovery period of at least two weeks. Experiments were started after a fasting period of 24 hours, during which water was available *ad libitum*. At the beginning of the experiment, the cannula was opened in order to remove any gastric juice or food remnants.

The stomach was cleansed with 40 to 50 ml lukewarm water. The test compound was administered I.V. (in a volume ≈ 3 ml via the vena cephalica), S.C. (in a volume ≈ 3 ml) or P.O. (in a volume of 1 ml/kg body weight, applied intragastrically via the cannula with a device that filled the lumen of the cannula; after injection of the test compound, 5 ml NaCl 0.9 % was injected in order to correct for the dead space in the injection system). Immediately after administration of the test compound or its solvent, lidamidine 0.63 mg/kg was administered subcutaneously. 30 Minutes later, the cannula was opened to determine the amount of fluid present in the stomach, promptly followed by reintroduction of the fluid. Then the test meal was administered via the cannula. This test meal consisted of 250 ml distilled water containing glucose (5 g/l) as a marker. The cannula remained closed for 30 min, whereafter the gastric contents were drained from the stomach to measure total volume (t = 30 minutes). For later analysis 1 ml of the gastric contents was taken, promptly followed by reintroduction of the rest volume into the stomach. This sequence was repeated 4 times with 30 minutes intervals (t = 60, 90, 120, 150 minutes).

In the 1 ml samples of the gastric contents, the glucose concentrations were measured on a Hitachi 717 automatic analyser by the hexokinase method (Schmidt, 1961). These data were used to determine the absolute amount of glucose that remained in the stomach after each 30 min period, as a measure for the rest volume of the meal itself, independent of acid secretion.

Curves were fitted to the measurement points (glucose vs time) using weighed non-linear regression analysis. Gastric emptying was quantified as the time needed to empty 70% of the meal ($t_{70\%}$). The control emptying time was calculated as the mean $t_{70\%}$ of the last 5 solvent experiments of the same dog. Acceleration of delayed gastric emptying (Δt) was calculated as the time difference between $t_{70\%\ compound}$ and $t_{70\%\ solvent}$. To correct for variations in emptying rate between dogs, Δt was expressed as % of $t_{70\%\ solvent}$ (Schuurkes et al, 1992).

Table 5 :

Acceleration of gastric emptying of a liquid meal delayed by lidamidine in conscious dog with a dose of 0.04 mg/kg of the test compound.

Co. No.	Acceleration (Δt/t)	Co. No.	Acceleration (Δt/t)
4	-0.40	11	-0.54
6	-0.41	12	-0.48
2	-0.34	13	-0.28
7	-0.54	10	-0.30
3	-0.30	14	-0.43
5	-0.51	18	-0.27
9	-0.60		

D. Composition examples

The following formulations exemplify typical pharmaceutical compositions in dosage unit form suitable for systemic or topical administration to warm-blooded animals in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable acid or base addition salt or a stereochemically isomeric form thereof.

Example D.1 : Oral solutions

9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxybenzoate are dissolved in 4 l of boiling purified water. In 3 l of this solution are dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of the A.I. The latter solution is combined with the remaining part of the former solution and 12 l of 1,2,3-propanetriol and 3 l of sorbitol 70% solution are added thereto. 40 g of sodium saccharin are dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence are added. The latter solution is combined with the former, water is added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the A.I. per teaspoonful (5 ml). The resulting solution is filled in suitable containers.

Example D.2 : Capsules

20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate are vigorously stirred together. The resulting mixture is subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 20 mg of the A.I..

Example D.3 : Film-coated tablets

Preparation of tablet core

A mixture of 100 g of the A.I., 570 g lactose and 200 g starch is mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinyl-pyrrolidone in about 200 ml of water. The wet powder mixture is sieved, dried and sieved again. Then there are added 100 g microcrystalline cellulose and 15 g hydrogenated vegetable oil. The whole is mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

To a solution of 10 g methyl cellulose in 75 ml of denaturated ethanol there is added a solution of 5 g of ethyl cellulose in 150 ml of dichloromethane. Then there are added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol is molten and dissolved in 75 ml of dichloromethane. The latter solution is added to the former and then there are added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concen-trated colour suspension and the whole is homogenated. The tablet cores are coated with the thus obtained mixture in a coating apparatus.

Example D.4 : Injectable solution

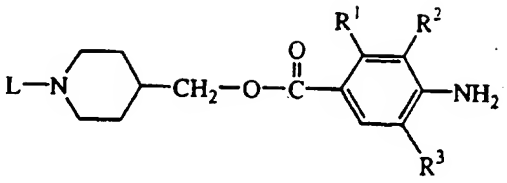
1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg/ml of A.I. The solution was sterilized by filtration and filled in sterile containers.

Example D.5 : Suppositories

3 Grams A.I. was dissolved in a solution of 3 grams 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 Grams surfactant and 300 grams triglycerides were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37-38°C to form 100 suppositories each containing 30 mg/ml of the A.I.

Claims.

1. A compound of formula



(I'),

the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R^1 is C_{1-6}alkyloxy, C_{2-6}alkenyloxy or C_{2-6}alkynyloxy;

R^2 is hydrogen or C_{1-6}alkyloxy,

or when taken together R^1 and R^2 may form a bivalent radical of formula

-O-CH_2-O- (a-1),

-O-CH_2-CH_2- (a-2),

-O-CH_2-CH_2-O- (a-3),

-O-CH_2-CH_2-CH_2- (a-4),

-O-CH_2-CH_2-CH_2-O- (a-5),

-O-CH_2-CH_2-CH_2-CH_2- (a-6),

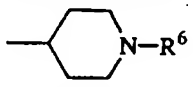
wherein in said bivalent radicals one or two hydrogen atoms may be substituted with C_{1-6}alkyl;

R^3 is hydrogen or halo;

L is C_{3-6}cycloalkyl, C_{5-6}cycloalkanone, C_{2-6}alkenyl optionally substituted with Ar, or L is a radical of formula

–Alk–R^4 (b-1),

–Alk–NR^5R^6 (b-2),

 (b-3),

-Alk-X-R^7 (b-4),

-Alk-Y-C(=O)-R^9 (b-5), or

-Alk-Y-C(=O)-$NR^{11}R^{12}$ (b-6),

wherein Alk is C_{1-12}alkanediyl;

R^4 is hydrogen, C_{1-6}alkylsulfonylamino, C_{3-6}cycloalkyl, C_{5-6}cycloalkanone, Ar-, di(Ar)methyl, Ar-oxy- or Het^1;

R^5 is hydrogen or C_{1-6}alkyl;

R^6 is Het^2;

R^7 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-6}cycloalkyl, Ar or Het^2;

X is O, S, SO_2 or NR^8; said R^8 being hydrogen, C_{1-6}alkyl or Ar;

R^9 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, Ar, ArC_{1-6}alkyl, di(Ar)methyl, C_{1-6}alkyloxy or hydroxy;

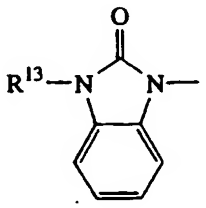
Y is NR^{10} or a direct bond; said R^{10} being hydrogen, C_{1-6}alkyl or Ar;

R^{11} and R^{12} each independently are hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, Ar or ArC_{1-6}alkyl, or R^{11} and R^{12} combined with the nitrogen atom bearing R^{11} and R^{12} may form a pyrrolidinyl or piperidinyl ring both being optionally substituted with C_{1-6}alkyl, amino or mono or di(C_{1-6}alkyl)amino, or said R^{11} and R^{12} combined with the nitrogen bearing R^{11} and R^{12} may form a piperazinyl or 4-morpholinyl radical both being optionally substituted with C_{1-6}alkyl;

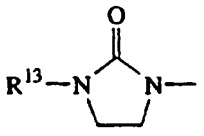
each Ar being unsubstituted phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino-sulfonyl, C_{1-6}alkylcarbonyl, nitro, trifluoromethyl, amino or aminocarbonyl; and

Het^1 and Het^2 each independently are selected from furan; furan substituted with C_{1-6}alkyl or halo; tetrahydrofuran; a tetrahydrofuran substituted with C_{1-6}alkyl; a dioxolane; a dioxolane substituted with C_{1-6}alkyl, a dioxane; a dioxane substituted with C_{1-6}alkyl; tetrahydropyran; a tetrahydropyran substituted with C_{1-6}alkyl; pyrrolidinyl; pyrrolidinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, or C_{1-6}alkyl; pyridinyl; pyridinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl; pyrimidinyl; pyrimidinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, amino and mono and di(C_{1-6}alkyl)amino; pyridazinyl; pyridazinyl substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, C_{1-6}alkyl or halo; pyrazinyl; pyrazinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, mono- and di(C_{1-6}alkyl)amino and C_{1-6}alkyloxycarbonyl;

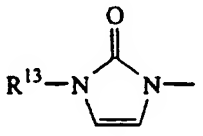
Het^1 can also be a radical of formula



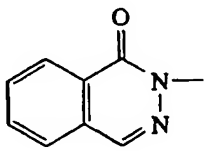
(c-1)



(c-2)

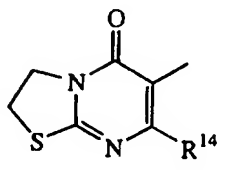


(c-3)

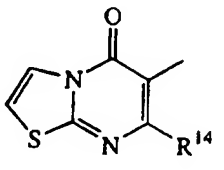


(c-4)

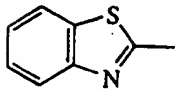
Het^1 and Het^2 each independently can also be selected from the radicals of formula



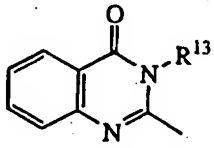
(d-1)



(d-2)



(d-3)



(d-4)

R^{13} and R^{14} each independently are hydrogen or C_{1-4}alkyl;

with the proviso that R^4 is other than hydrogen, phenyl, 4-fluorophenyl, 4-methylphenyl or 4-methoxyphenyl when R^1 and R^2 are taken together to form a bivalent radical of formula -O-CH_2-CH_2-O-; or L is other than n-butyl when R^1 and R^2 are taken together to form a bivalent radical of formula (a-2) or (a-4).

2. A compound according to claim 1 wherein R^1 is methoxy, R^2 is hydrogen or wherein R^1 and R^2 taken together form a radical of formula (a-2) or (a-3) and R^3 is chloro.

3. A compound according to claim 1 wherein L is a radical of formula (b-1) and R^4 is Het^1 or phenyloxy substituted with 1, 2 or 3 substituents each independently selected from halo, trihalomethyl, C_{1-6}alkyl or C_{1-6}alkyloxy.

4. A compound according to claim 1 wherein L is a radical of formula (b-2) or (b-3) and R^6 is Het^2.

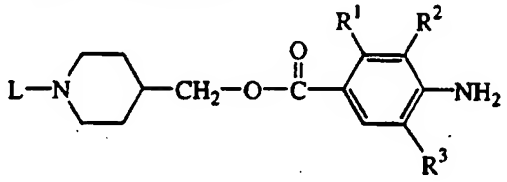
5. A compound according to claim 1 wherein L is a radical of formula (b-1), (b-2) or (b-3) wherein R^4 is phenyloxy substituted with halo, R^5 is hydrogen and R^6 is pyrazidinyl or imidazolyl optionally substituted with hydroxy or C_{1-3}alkyl.

6. A compound according to claim 1 wherein the compounds are
[1-[2-[(3-methyl-2-pyrazinyl)amino]ethyl]-4-piperidinyl]methyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; or
[1-[2-[2,3-dihydro-3-(1-methylethyl)-2-oxo-1H-imidazol-1-yl]ethyl]-4-piperidinyl]-methyl 4-amino-5-chloro-2,3-dihydro-7-benzofurancarboxylate; or
[1-[2-[(3-methyl-2-pyrazinyl)amino]ethyl]-4-piperidinyl]methyl 8-amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-carboxylate; or
[1-[1-(3-methyl-2-pyrazinyl)-4-piperidinyl]-4-piperidinyl]methyl 8-amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-carboxylate; the stereochemically isomeric

forms, pharmaceutically acceptable acid addition salts and the *N*-oxide forms thereof.

7. A compound according to any one of claims 1 to 6 for use as a medicine.

8. The use of a compound of formula (I)



(I);

the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R^1 is C_{1-6}alkyloxy, C_{2-6}alkenyloxy or C_{2-6}alkynyloxy;

R^2 is hydrogen or C_{1-6}alkyloxy,

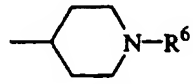
or when taken together R^1 and R^2 may form a bivalent radical of formula

-O-CH_2-O-	(a-1),
-O-CH_2-CH_2-	(a-2),
-O-CH_2-CH_2-O-	(a-3),
-O-CH_2-CH_2-CH_2-	(a-4),
-O-CH_2-CH_2-CH_2-O-	(a-5),
-O-CH_2-CH_2-CH_2-CH_2-	(a-6),

wherein in said bivalent radicals one or two hydrogen atoms may be substituted with C_{1-6}alkyl;

R^3 is hydrogen or halo;

L is C_{3-6}cycloalkyl, C_{5-6}cycloalkanone, C_{2-6}alkenyl optionally substituted with Ar, or L is a radical of formula

–Alk–R^4	(b-1),
–Alk–NR^5R^6	(b-2),
	(b-3),
-Alk-X-R^7	(b-4),
-Alk-Y-C(=O)-R^9	(b-5), or
-Alk-Y-C(=O)-$NR^{11}R^{12}$	(b-6),

wherein Alk is C_{1-12}alkanediyl;

R^4 is hydrogen, C_{1-6}alkylsulfonylamino, C_{3-6}cycloalkyl, C_{5-6}cycloalkanone, Ar-, di(Ar)methyl, Ar-oxy- or Het^1;

R^5 is hydrogen or C_{1-6}alkyl;

R^6 is Het^2;

R^7 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{3-6}cycloalkyl, Ar or Het^2;

X is O, S, SO_2 or NR^8; said R^8 being hydrogen, C_{1-6}alkyl or Ar;

R^9 is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, Ar, ArC_{1-6}alkyl, di(Ar)methyl, C_{1-6}alkyloxy or hydroxy;

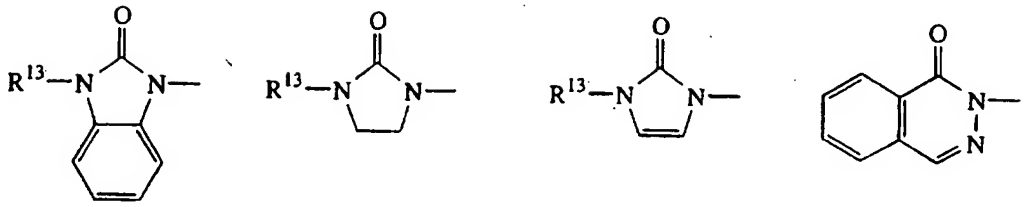
Y is NR^{10} or a direct bond; said R^{10} being hydrogen, C_{1-6}alkyl or Ar;

R^{11} and R^{12} each independently are hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, Ar or ArC_{1-6}alkyl, or R^{11} and R^{12} combined with the nitrogen atom bearing R^{11} and R^{12} may form a pyrrolidinyl or piperidinyl ring both being optionally substituted with C_{1-6}alkyl, amino or mono or di(C_{1-6}alkyl)amino, or said R^{11} and R^{12} combined with the nitrogen bearing R^{11} and R^{12} may form a piperazinyl or 4-morpholinyl radical both being optionally substituted with C_{1-6}alkyl;

each Ar being unsubstituted phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino-sulfonyl, C_{1-6}alkylcarbonyl, nitro, trifluoromethyl, amino or aminocarbonyl; and

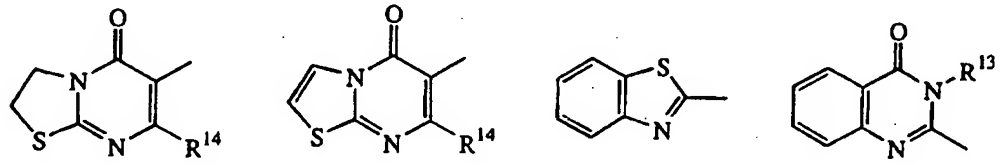
Het^1 and Het^2 each independently are selected from furan; furan substituted with C_{1-6}alkyl or halo; tetrahydrofuran; a tetrahydrofuran substituted with C_{1-6}alkyl; a dioxolane; a dioxolane substituted with C_{1-6}alkyl, a dioxane; a dioxane substituted with C_{1-6}alkyl; tetrahydropyran; a tetrahydropyran substituted with C_{1-6}alkyl; pyrrolidinyl; pyrrolidinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, or C_{1-6}alkyl; pyridinyl; pyridinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl; pyrimidinyl; pyrimidinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, amino and mono and di(C_{1-6}alkyl)amino; pyridazinyl; pyridazinyl substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, C_{1-6}alkyl or halo; pyrazinyl; pyrazinyl substituted with one or two substituents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, mono- and di(C_{1-6}alkyl)amino and C_{1-6}alkyloxycarbonyl;

Het^1 can also be a radical of formula



(c-1) (c-2) (c-3) (c-4)

Het^1 and Het^2 each independently can also be selected from the radicals of formula



(d-1) (d-2) (d-3) (d-4)

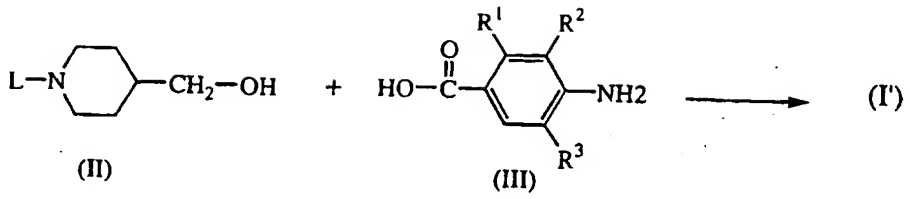
R^{13} and R^{14} each independently are hydrogen or C_{1-4}alkyl;
with the proviso that L is other than n-butyl when R^1 and R^2 are taken together to form a bivalent radical of formula (a-2);
for the manufacture of a medicine for treating conditions involving a decreased motility of the stomach.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as claimed in any one of claims 1 to 6.

10. A process for preparing a pharmaceutical composition as claimed in claim 9 characterized in that a therapeutically active amount of a compound as claimed in any one of claims 1 to 6 is intimately mixed with a pharmaceutically acceptable carrier.

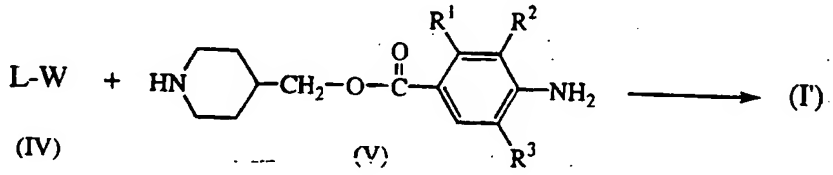
11. A process for preparing a compound of formula (I') characterized by

a) reacting an intermediate of formula (II) with an carboxylic acid derivative of formula (III) or a reactive functional derivative thereof, such as for example an acid chloride,



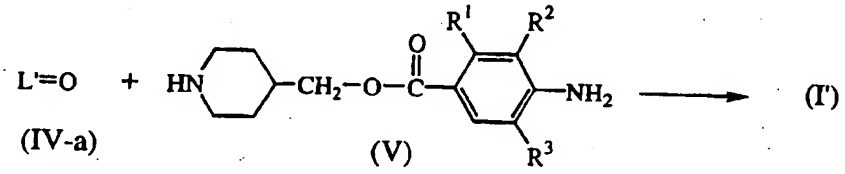
(II) (III) (I')

b) *N*-alkylating an intermediate of formula (IV), wherein W represents an appropriate leaving group such as halo, with a reagent of formula (V).



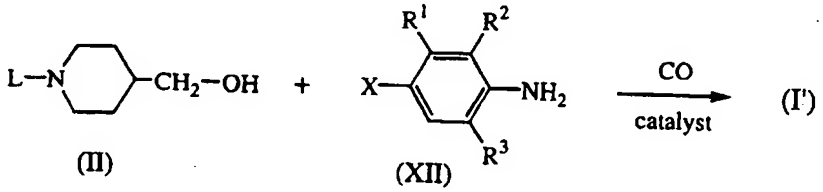
(IV) (V) (I')

c) reacting an appropriate ketone or aldehyde intermediate of formula L'=O (IV-a), said L'=O represents a derivative of formula L–H wherein two geminal hydrogen atoms are replaced by oxygen, with a piperidine of formula (V)



(IV-a) (V) (I')

d) carbonylating an intermediate of formula (XII), wherein X is bromo or iodo, in the presence of an intermediate of formula (II)



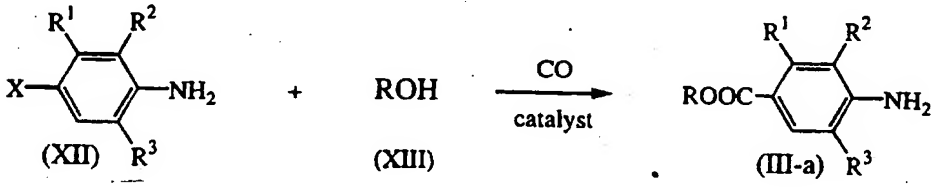
(II) (XII) (I')

in a reaction-inert solvent such as, e.g. acetonitrile or tetrahydrofuran, in the presence of a suitable catalyst, such as palladium-on-carbon, and a tertiary amine such as, e.g. triethylamine, and at a temperature ranging between room temperature and the reflux temperature of the reaction mixture,

and, if desired, converting compounds of formula (I) into each other following art-known transformations; and further, if desired, converting the compounds of formula (I'), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or conversely, converting the acid addition salt form

into the free base by treatment with alkali; and, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.

12. A process for preparing a compound of formula (III-a), wherein R^1, R^2, and R^3 are as defined in claim 1 and R is C_{1-6}alkyl, characterized by carbonylating an intermediate of formula (XII), wherein X is bromo or iodo, with an alcohol of formula (XIII), wherein R is C1-6alkyl,



in a reaction-inert solvent such as, e.g. acetonitrile or tetrahydrofuran, in the presence of a suitable catalyst, such as palladium-on-carbon, and potassium acetate or a tertiary amine such as, e.g. triethylamine, and at a temperature ranging between room temperature and the reflux temperature of the reaction mixture.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT 97/00585

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/22 C07D401/12 C07D401/06 C07D405/12 C07D405/14
C07D401/14 C07D417/14 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 96 33186 A (PHARMACIA S.P.A., ITALY) 24 October 1996 cited in the application see claim 1; example 2 ---	1,7-11
P,X	WO 96 28424 A (BOEHRINGER INGELHEIM ITALIA S.P.A., ITALY) 19 September 1996 cited in the application see claim 1 --- -/--	1,7-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 1997	24.04.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Kissler, B

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X	WO 93 03725 A (SMITHKLINE BEECHAM PLC, UK) 4 March 1993 see claim 1	1-3,7-11
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